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WORKGROUP ON COMPOUNDING

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Empire Room, Building 5

MEETING MATERIALS

Attachment A — Concept Draft on General Compounding

Attachment B — Report from the Subcommittee on Law

- Recommendations on FDA Compliance Policy
- Definition of Manufacturing and Compounding
- Factors to be Considered by Board Inspectors (2 documents)

ATTACHMENT A

CONCEPT DRAFT
GENERAL COMPOUNDING

Part 1 - Definitions

(a) "Compounding" means any the following activities occurring in a pharmacy:
(1) Altering the dosage form or delivery system of a drug.
(2) Altering the strength of a drug.
(3) Combining active ingredients.
(4) Preparing a drug from bulk chemicals.

(b) "Strength" means the amount of active ingredient in each unit of the drug.

(c) "Quality" means the drug is free of any contaminants only contains those active ingredients indicated on the label.

(d) "Integrity" means the drug will retain its effectiveness until the beyond use date noted on the label.

Part 2 – Requirements

(a) Prior to compounding a drug, the pharmacist shall establish a professional relationship with the prescriber and patient.

(b) A drug may not be compounded without a written master formula record that includes at least the following elements:

(1) Active ingredients to be used.
(2) Inactive ingredients to be used.
(3) Process and/or procedure used to prepare the drug.
(4) Quality reviews required at each step in preparation of the drug.
(5) Post compounding process or procedures required, if any.
(6) Beyond use dating requirements.

(c) The pharmacist shall assure that the compounded drug retains its strength, quality, and integrity.

(d) All chemicals, drug products, and components must be used and stored according to compendial and other applicable requirements to maintain their strength, quality and integrity.

(e) The expiration date of the finished product must not exceed 180 days or the shortest expiration date of any component in the finished product unless a longer date is supported by stability studies in the same type of packaging as furnished to the prescriber. Shorter dating than set forth in this subsection may be used if it is deemed appropriate in the professional judgment of the responsible pharmacist.

(f) A pharmacy may contract with another pharmacy to compound non-sterile drug products, pursuant to a prescription, for delivery to another pharmacy. The compounded product must be labeled with the following:

(1) the name of the pharmacy that compounded the drug
(2) the name of the pharmacy that dispensed the drug to the patient in addition
(3) the information required by Business and Professions Code Section 4076.

(g) Pharmacists who compound drugs, or supervise the compounding of drugs, shall be responsible for ensuring that the compounded drug has been prepared, labeled, stored, and delivered properly.

(h) Prior to allowing any drug to be compounded in a pharmacy, the pharmacist-in-charge shall complete a self-assessment form for compounding pharmacies developed by the board. The self assessment shall subsequently be performed before July 1 of every odd-numbered year, within 30 days of the designation of a new pharmacist-in-charge, or within 30 days of the issuance of a new pharmacy permit.. The primary purpose of the self-assessment is to promote compliance through self-examination and education.

Part 3 – Records

(a) For each compounded drug a record shall be made that includes at least the following elements:

(1) The information required of a master formula record.
(2) The date the drug was compounded.
(3) The identity of the pharmacy personnel who compounded the drug.
(4) The identity of the pharmacist reviewing the final product.
(5) The quantity of each component used compounding a drug.
(6) The supplier and lot number of each component.
(7) The equipment used compounding a drug.
(8) The internal reference (lot) number.
(9) The expiration date of the final drug.

(c) Pharmacies must maintain written records of the acquisition, storage, and proper destruction of chemicals, drug products, and components used in compounding.

(d) Documentation must be maintained that the chemicals, drug products, and components have been procured from reliable suppliers and certificates of purity or analysis must accompany chemical purchases and be retained in the pharmacy.

(e) Pharmacies must prepare, maintain, and retain all records required by this act for a period of three years from the date the record was created.

Part 4 - Labeling

(a) In addition to labeling information required under Businesss and Professions Code Section 4076, the label of a compounded drug product shall contain the generic name(s) of the principal active component(s).

(b) A statement that the drug has been compounded by the pharmacy shall be included on the container (auxiliary label may be used).

(c) Drugs compounded into unit-of-use containers shall be labeled with the name of the active component, concentration or strength, volume or weight, and an expiration date.

Part 5 - Policies and Procedures

(a) Pharmacies must provide written documentation of a compounding policy and procedure manual that establishes procurement procedures, methodologies for the formulation and compounding of drugs, facilities and equipment cleaning, maintenance, operation, and other standard operating procedures for the facility.

(b) The policy and procedure manual shall be reviewed on an annual basis by the pharmacist-in-charge.

(c) Provisions to notify the staff assigned compounding duties of any changes in the policy and procedure manual must also be included.

(d) The policy and procedure manual must also include written documentation of a plan for the recall of dispensed compounded products where subsequent verification demonstrates the potential for adverse effects with continued use of the compounded drug.

(e) Written processes used to maintain, store, calibrate, clean/disinfect equipment used in compounding drug shall be contained in the policy and procedure manual and shall be incorporated as part of the staff training and competency evaluation process.

(f) The pharmacist-in-charge shall establish policies and procedures to ensure that compounded drugs have the strength indicated by the label.

(g) The policies and procedures shall include procedures for the recall of compounded drugs.

Part 6 - Facilities and Equipment

(a) Pharmacies must provide written documentation of facilities and equipment necessary for the safe and accurate compounding of a drug, to also include, where applicable, certification of the facility/equipment.

(b) Equipment must be stored, used, and maintained in accordance with manufacturers specifications.

(c) Equipment used in compounding drug products are to be calibrated prior to use to ensure retained accuracy. Documentation of calibration shall be recorded in a written format to include but limited to where applicable, temperature, weight, volume, etc.

Part 7 - Training of Staff, Patient and Caregiver

(a) Pharmacies must provide written documentation that pharmacy personnel have the skills and training required to correctly understand and perform their assigned responsibilities relating to compounding.

(b) The training of pharmacy personnel shall be documented and retained as part of an on-going competency evaluation process for pharmacy personnel involved in compounding.

(c) Pharmacy personnel assigned compounding duties shall demonstrate knowledge about the processes and procedures used to compound drug drugs prior to compounding any drug.

Part 8 - Quality Assurance

(a) Pharmacies must provide written documentation of the development of and adherence to a quality assurance plan.

(b) The quality assurance plan must include verification, monitoring, and review of the adequacy of the compounding process and must include documentation of that review by the assigned personnel to demonstrate the compounded drug meets the specified criteria of strength and quality.

(c) As part of the quality assurance plan, all qualitiative/quantitative analysis reports for compounded drug drugs must be retained and collated with the compounding record and master formulation.

(d) The quality assurance plan shall also include a written process that describes and documents the action taken when a compounded drug fails to meet the minimum standards for quality, strength and integrity.

ATTACHMENT B

Guidance for FDA Staff and Industry
Compliance Policy Guides
Section 460.200 Pharmacy Compounding

"In determining whether to initiate such an action, the Agency will consider whether the pharmacy engages in any of the following acts:"

1. "Compounding of drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions."

Recommendation: Do not consider for California CPGs

Comments:
California Code of Regulations 1716.2. specifically allows compounding in anticipation of receiving prescriptions. Pharmacies are businesses. Pharmacies strive to provide good customer service. Making compounded medications available in a timely manner is both good customer service; and, oftentimes, is critical to the well-being of that patient.

Compounded sterile injectables should be tested for the presence of endotoxin and sterility. These tests require two weeks to obtain the final results for sterility. It is not practical nor is it good therapy for a patient to bring in an urgently needed medication and then be told it will be at least two weeks before they can obtain it. The FDA guidance should take these concerns into account for compounds with a history of use and, in addition, consider that some prescriptions must be filled immediately and prior to final test results under some circumstances.

When there is a history of receiving prescriptions for a particular product, it is logical to allow anticipatory compounding in order to have the product available when the patient needs it.

2. "Compounding drugs that were withdrawn or removed from the market for safety reasons. Appendix A provides a list of such drugs that will be updated in the future, as appropriate."

Recommendation: Do not consider for California CPGs
Comments:
Appendix A is an obsolete list. Committee to review has been disbanded.

3. "Compounding finished drugs from bulk active ingredients that are not components of FDA approved dugs without an FDA sanctioned investigational new drug application (IND) in accordance with 21 U.S.C. S 355(i) and 21 CFR 312."

Recommendation: Do not consider for California CPGs
Comments:

The Food and Drug Administration Modernization Act of 1997 had a Bulk Drugs List of bulk substances permissible for use in pharmacy compounding. The list was useful but is now obsolete.

Components of "grandfathered" commercial drugs, e.g. Dexpanthenol, should be allowed.

Components required to prepare drugs complying with any monograph in the USP should be allowed.

4. "Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility."

Recommendation: Do not consider for California CPGs
Comments:
A Certificate of Anaylsis should be required instead.

5. "Receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements."

Recommendation: Do not consider for California CPGs
Comments:
There are many products needed by patients that are not included in the official compendia.

6. "Using commercial scale manufacturing or testing equipment for compounding drug products."

Recommendation: Do not consider for California CPGs

Comments:

Pharmacies should be encouraged to use compounding and testing equipment that will result in high quality products.

7. "Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale."

Recommendation: Modify as such:

Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale except as permitted by B&P Code 4123 and CCR 1716.1.

8. "Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products. In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an FDA-approved drug that is commercially available. In these circumstances, FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient."

Recommendation: Modify as such:

The pharmacy is compounding products the same as FDA approved products that are commercially available in dosage form, strength, concentration, route of administration, and performance characteristics."

9. "Failing to operate in conformance with applicable state law regulating the practice of pharmacy."

Recommendation: Modify as such:

Failing to be licensed in those states where deliver would require a license.

Definitions:

1. B&P Code 4033. Manufacturer, Manufacturing
   - (a) "Manufacturer" means and includes every person who prepares, derives, produces, or repackages any drug or device except a pharmacy that manufactures on the immediate premises, where the drug or device is sold to the ultimate consumer. [1]
   - (b) Notwithstanding subdivision (a), manufacturer shall not mean a pharmacy compounding a drug pursuant to a prescription, for delivery to another pharmacy for the purposes of delivering or administering the drug to the patient or patients. [2,3]
   - (c) Notwithstanding subdivision (a), manufacturer: shall not mean a pharmacy that, at a patient's request, repackages a drug previously dispensed to the patient, or to the patient's agent, pursuant to a prescription.
   - (d) Manufacturing is defined as preparing, deriving, producing, or repackaging any drug or device. [4]
2. B&P Code 4037. Pharmacy, Compounding
   - (a) "Pharmacy" means an area, place, or premise licensed by the board in which the profession of pharmacy is practiced and where prescriptions are compounded. "Pharmacy" includes but is not limited to, any area, place, or premise described in a license issued by the board wherein controlled substances, dangerous drugs, or dangerous devices are stored, possessed, prepared, manufactured, derived, compounded, or repackaged, and from which the controlled substance, dangerous drugs, or dangerous devices are furnished, sold, or dispensed at retail.
   - (b) "Pharmacy" shall not include any area in a facility licensed by the State department of Health Services where floor supplies, ward supplies, operating room supplies, or emergency room supplies of dangerous drugs or dangerous devices are stored or possessed solely for treatment of patients registered for treatment in the facility or for treatment of patients receiving emergency care in the facility.
   - (c) Compounding is manufacturing performed within the scope of pharmacy practice. [5]

1. Remove "compounds" from definition. Reserve this term for pharmacy scope of practice.
2. Remove "for parenteral therapy". Facilitates delivery of non-parenteral therapy to another pharmacy.
3. Remove "provided that neither the components for the drug nor the drug are compounded, fabricated, packaged, or otherwise prepared prior to receipt of the prescription. Pharmacy law allows anticipatory compounding and is essential to allow final product testing, e.g. 14 day sterility testing.
4. Adds definition of manufacturing.
5. Adds definition of compounding.

Factors to Be Considered by the Board of Pharmacy Inspectors

The following factors will be considered by the board inspectors as suggesting that a pharmacy which claims to be compounding is actually engaged in manufacturing which is beyond the scope of its pharmacy permit.

1. A professional relationship does not exist among the prescriber, patient and pharmacist who compounds and dispenses the drug product. Retained and clarified.

2. The pharmacy solicits or advertises for business from any practicioners or other entity for specific products which the pharmacy compounds. Deleted: the U.S. Supreme Court has declared this factor unconstitutional.

3. The pharmacy is compounding products which are essentially generic copies of FDA approved products which are commercially available. Retained and clarified.

4. The pharmacy is receiving and using drug substances or components without obtaining and retaining appropriate evidence of source or methods of preparation.
   Deleted: Obtaining a certificate of analysis or other evidence of source or method of preparations is the responsibility of both a compounding pharmacy and a manufacturer and whether or not this quality standard is met does not differentiate a compounder from a manufacturer.

5. The pharmacy is compounding drugs in anticipation of receiving prescriptions, as opposed to in response to individual prescriptions. The volume of such drugs compounded by the pharmacy is high when compared to the volume of prescriptions actually received for such drugs.
   Deleted: Any arbitrary volume limitation on compounding is senseless. Depending on the condition to be treated, the number of patients sharing the need for a compounded drug can be substantial. Any arbitrary volume limitation would let the first patent(s) benefit, while senselessly excluding later patents.
   Beyond-use date of products and historical prescribing practices should be the only limitation to anticipatory compounding. In addition, good business practices should naturally regulate anticipatory compounding and dictate the proper balance between efficiency and maintenance of minimum amount of stock. As anticipatory compounding is otherwise regulated, this factor should not be used to distinguish between compounding and manufacturing.

6. A significant amount of compounded drugs is distributed to patients or customers outside the pharmacy's normal trade area or across state lines.
   Modified as such: Failing to be licensed in those states where deliver would require a license.

7. Dugs are compounded by one pharmacy and dispensed by another pharmacy.
   Modified as such: Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale except as permitted by B&P Code 4123 and CCR 1716.1.

8. The pharmacy is not in general compliance with state or federal requirements for the production, preparation and maintenance of safe and effective drugs products.
   Deleted: This factor does not distinguish between compounding and manufacturing.

Factors to Be Considered by the Board of Pharmacy Inspectors

The board inspectors will consider several factors that may suggest that a pharmacy that claims to be compounding is actually engaged in manufacturing.

Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling.

Quality and quantity are not factors to be used in determining whether compounding is within the scope of practice of pharmacy.

- Producing high quality products is a common goal of compounding and manufacturing.
- Quality of preparations has no bearing on whether a pharmacy has gone beyond the scope of pharmacy practice. Our group believes that every pharmacy and every manufacturer has a moral and legal obligation to maintain quality. Standards for good compounding practices need to be met by pharmacies just as good manufacturing practices must be met by manufacturers. The degree to which each meets these standards of practice has no bearing on whether they are classified as a pharmacy or manufacturer.
- Any arbitrary volume limitation on compounding is senseless. Depending on the condition to be treated, the number of patients sharing the need for a compounded drug can be substantial. Any arbitrary volume limitation would let the first patent(s) benefit, while senselessly excluding later patents.
- Beyond-use date of products and historical prescribing practices should be the only limitation to anticipatory compounding. In addition, good business practices should naturally regulate anticipatory compounding and dictate the proper balance between efficiency and maintenance of minimum amount of stock. As anticipatory compounding is otherwise regulated, this factor should not be used to distinguish between compounding and manufacturing.

The board inspectors will consider the following factors that may suggest that a pharmacy that claims to be compounding is actually engaged in manufacturing.

1. "A professional relationship does not exist among the prescriber, patient and pharmacist who compounds and dispenses the drug product." A professional relationship is said to exist if a physician issues a prescription, issues an order for Office Use. A professional relationship is not necessary if the pharmacy is in compliance with B&P Code 4123.

2. "The pharmacy is compounding products the same as FDA approved products that are commercially available in dosage form, strength, concentration, route of administration, and performance characteristics."

   Pharmacies may compound drugs that were previously available commercially but are not readily available in the market or have been removed from the market for reasons other than safety or efficacy. In addition, pharmacies may compound products that are temporarily unavailable from the manufacturer, e.g. when the manufacturer is back ordered. When this occurs, the prescriber must be notified and made aware that a compounded preparation is being dispensed.

3. Failing to be licensed in those states where deliver would require a license.

4. Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale except as permitted by B&P Code 4123 and CCR 1716.1.

This list is not exhaustive; other factors may be considered on a case-by-case basis.

FDA has no jurisdiction in determining what factors distinguish compounding from Manufacturing, reference 21 U.S.C. section 360(g)(1) and section (a)(2)(A).